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ORIGINAL REPORT

# Peripheral Neuropathy, Sensory Processing, and Balance in Survivors of Acute Lymphoblastic Leukemia

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## ABSTRACT

### Purpose

To compare peripheral nervous system function and balance between adult survivors of childhood acute lymphoblastic leukemia (ALL) and matched controls and to determine associations between peripheral neuropathy (PN) and limitations in static balance, mobility, walking endurance, and quality of life (QoL) among survivors.

### Patients and Methods

Three hundred sixty-five adult survivors of childhood ALL and 365 controls with no cancer history completed assessments of PN (modified Total Neuropathy Score [mTNS]), static balance (Sensory Organization Test [SOT]), mobility (Timed Up and Go), walking endurance (6-minute walk test), QoL (Medical Outcomes Study 36-Item Short Form Survey), and visual-motor processing speed (Wechsler Adult Intelligence Scale).

### Results

PN, but not impairments, in performance on SOT was more common in survivors than controls (41.4% *v* 9.5%, respectively; $P < .001$). In multivariable models, higher mTNS scores were associated with longer time to complete the Timed Up and Go ($\beta = 0.15$; 95% CI, 0.06 to 0.23; $P < .001$), shorter distance walked in 6 minutes ($\beta = -4.39$; 95% CI, −8.63 to −0.14; $P = .04$), and reduced QoL ($\beta = -1.33$; 95% CI, −1.79 to −0.87; $P < .001$ for physical functioning; $\beta = -1.16$; 95% CI, −1.64 to −0.67; $P < .001$ for role physical; and $\beta = -0.88$; 95% CI, −1.34 to −0.42; $P < .001$ for general health). Processing speed ($\beta = 1.69$; 95% CI, 0.98 to 2.40; $P < .001$), but not mTNS score, was associated with anterior-posterior sway on the SOT.

### Conclusion

PN in long-term ALL survivors is associated with movement, including mobility and walking endurance, but not with static standing balance. The association between processing speed and sway suggests that static balance impairment in ALL survivors may be influenced by problems with CNS function, including the processing of sensory information.

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## INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer.[1] Risk-directed treatment strategies have improved 5-year survival in developed countries to > 85%,[2] with approximately 70,000 survivors of childhood ALL living in the United States.[1] However, improved survival does not come without cost. Survivors of pediatric ALL are at risk for developing late effects that negatively affect function, limit participation in activities, and reduce quality of life (QoL).[3-5]

Many adverse outcomes observed in cancer survivors are associated with specific treatment exposures, including the association between vincristine chemotherapy and peripheral neuropathy (PN).[6,7] PN manifests as decreased muscle strength, particularly in the distal lower extremities, and limited ankle range of motion.[8-10] Loss of ankle mobility and strength may negatively affect balance, which in turn may limit daily mobility and participation in usual activities.[11,12] The extent to which these impairments influence function and QoL in survivors of ALL has been investigated[13] but on a limited basis. Therefore, the primary objectives of this study were to compare PN and static balance in adult survivors of childhood ALL with sex-, race-, and age-matched controls and determine associations

ASSOCIATED CONTENT

Appendix

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between PN and limitations in static balance, mobility, walking endurance, and QoL among survivors.

## PATIENTS AND METHODS

Participants were members of the St Jude Lifetime study, which examines health outcomes among aging survivors of childhood cancer. Survivors were ≥ 10 years since primary cancer diagnosis, ≥ 18 years of age, treated for childhood ALL between January 1, 1980, and December 31, 2003, and cancer free at the time of assessment. Among 416 potentially eligible ALL survivors, 365 (87.7%) agreed to and 51 declined participation. A comparison group (controls) frequency matched with survivors on sex, race, and age (within 5 years) was recruited from friends, relatives, and family members of other patients at St Jude Children's Research Hospital. Of 451 potential controls, 365 (80.9%) agreed to and 86 declined participation (Fig 1). The protocol was approved by the St Jude Children's Research Hospital institutional review board, and all the participants provided informed consent.

### Measures

*Outcomes.* Static balance was characterized with the Sensory Organization Test (SOT), which uses computerized dynamic posturography (NeuroCom SMART EquiTest; Natus Medical, Pleasanton, CA)[14,15] to evaluate postural sway (ability to maintain upright in a 12° sway envelope) under six conditions. Conditions 1 to 3 have a fixed standing surface and are done with eyes open, eyes closed, and eyes open but sway referenced (visual surround moves in reference to anterior-posterior sway). Conditions 4 to 6 are the same but with a sway-referenced standing surface (the force plate moves in reference to anterior-posterior sway). Two or three trials (20 seconds long) were collected for each condition. Scores from the six conditions were used to derive an overall SOT score. For this study, similar to a previous St Jude Lifetime study,[9] participants with an SOT score 1.5 standard deviations below the control mean (< 74.43) were classified as having impaired balance (on the basis of a standard normal distribution, 6.7% of a healthy population would score < 74.43). The ability of participants to use sensory inputs to control balance was also evaluated using performance ratios calculated from various test conditions: somatosensory ratio (condition 2/condition1), vision ratio (condition 4/condition1), and vestibular ratio (condition 5/condition 1).

Mobility was assessed with the Timed Up and Go (TUG) test.[16,17] Participants rose from a standard armchair, walked to a line 10 feet away, turned, returned, and sat down while encouraged to complete this task as fast as possible. Two trials were attempted; the time to complete the second trial was used for the analysis. Walking endurance was evaluated with the 6-minute walk test.[18,19] Participants walked as fast as possible along a corridor for 6 minutes. Customary walking aids (canes, walkers, crutches) were allowed; distance was recorded in meters.

QoL was measured with the Medical Outcomes Study 36-Item Short Form Survey, which includes questions about health and well-being over the previous 4 weeks.[20] In this study, we only used the physical functioning, role physical, and general health subscales of this survey. Results are reported as T scores, with a population mean of 50 and a standard deviation of 10. Higher scores indicate better QoL.

*Independent variables.* Sensory and motor integrity were evaluated with the modified Total Neuropathy Score (mTNS).[21] This test assesses sensory and motor symptoms and evaluates distal muscle strength, deep tendon reflexes, light touch sensation, and vibration threshold. Results range from 0 (no neuropathy) to 24 (severe neuropathy). Although even a score of 1 indicates the presence of neuropathy,[22,23] we used a score 1.5 standard deviations above the control mean (mTNS ≥ 4) to classify neuropathy—an approach used in previous studies of PN among pediatric and adult ALL survivors.[9,24]

Active ankle dorsi- and plantar-flexion range of motion were measured with a goniometer[25] while sitting, with the hips and knees in 90° of flexion. System 4 (Biodex, Shirley, NY)[26] was used to measure peak isokinetic ankle dorsi- and plantar-flexor strength at 60° per second and endurance at 90° per second.

Visual-motor processing speed (VMPS) in survivors was evaluated with the digit symbol coding test from the Wechsler Adult Intelligence Scale–Fourth Edition.[27] Scores were transformed into age-adjusted *z* scores with a population mean of 0 and a standard deviation of 1.

Smoking status and the presence of type 2 diabetes that requires medication were determined by self-report. Treatment data were abstracted from medical records.

### Analyses

Demographics were compared between survivors and controls using the *t* or $\chi^2$ test. Measures of PN, balance, and QoL were compared between survivors and matched controls in linear models adjusted for height and smoking status. *t* tests were used to compare static balance, mobility, walking endurance, and QoL between survivors with and without PN and to compare SOT score sensory ratios between survivors with and without impaired balance. To address the increased risk of committing type I error associated with multiple comparisons, α-levels were corrected using Bonferroni's method.[28] Associations between mTNS and static balance, mobility, walking endurance, QoL, and sensory ratios in survivors, adjusting for age at assessment, sex, body mass index (BMI), history of cranial radiation treatment (CRT), and VMPS, were evaluated using linear regression models. SPSS version 22 statistical software (IBM Corporation, Chicago, IL) was used for analyses.

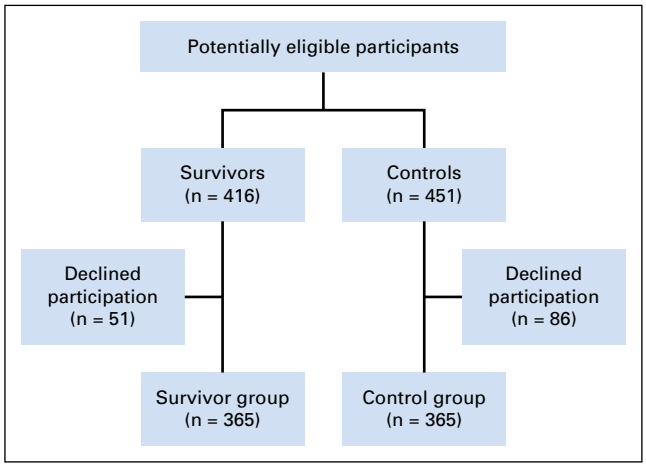


**Fig 1.** Participant flow diagram.

## RESULTS

Participant characteristics are listed in Table 1. Survivors were shorter, and male survivors had a higher mean BMI than controls. All survivors were exposed to vincristine and intrathecal methotrexate; 40.8% had received CRT. Group comparisons of mTNS, SOT score, and QoL, adjusted for height and smoking status, are listed in Table 2. Mean score on the mTNS was higher among survivors, and more survivors were classified with PN than controls (41.4% *v* 9.5%; $P < .001$). In survivors with PN, mean mTNS was 5.26 (*v* 1.48 in survivors without PN). Motor symptoms were uncommon in survivors who scored < 4 on the mTNS (Appendix Table A1, online only). Smoking was identified as a significant risk factor (Appendix Table A2, online only) for PN. A test for

  

**Table 1.** Participant Characteristics

| Characteristic | Survivors (N = 365) | Controls (N = 365) | *P* |
|---|---|---|---|
| Mean age, years (SD) | 28.6 (5.9) | 29.0 (7.5) | .480 |
| Sex | | | 1.000 |
| Male | 191 (52.3) | 191 (52.5) | |
| Female | 174 (47.7) | 174 (47.5) | |
| Race | | | 1.000 |
| White | 317 (86.8) | 317 (86.8) | |
| Black | 44 (12.1) | 44 (12.1) | |
| Other | 4 (1.1) | 4 (1.1) | |
| Mean height, cm (SD) | | | |
| Male | 174.7 (8.2) | 178.9 (7.0) | < .001 |
| Female | 161.7 (7.3) | 164.2 (5.4) | < .001 |
| Mean weight, kg (SD) | | | |
| Male | 87.7 (22.2) | 87.3 (19.1) | .830 |
| Female | 74.9 (21.3) | 74.9 (22.2) | .990 |
| Mean body mass index, kg/m$^2$ (SD) | | | |
| Male | 28.6 (6.4) | 27.2 (5.6) | .030 |
| Female | 28.6 (7.8) | 27.8 (8.0) | .330 |
| Smoking status | | | .380 |
| Current | 91 (24.9) | 99 (27.8) | |
| Former | 38 (10.4) | 37 (10.4) | |
| Nonsmoker | 238 (64.7) | 220 (61.8) | |
| Diabetes status* | | | .750 |
| With diabetes | 6 (1.7) | 4 (1.2) | |
| Without diabetes | 355 (98.3) | 337 (98.8) | |
| Treatment | | | |
| Cranial irradiation | 149 (40.8) | | |
| Median vincristine dose, mg/m$^2$ (range) | 47.0 (3.3-105.3) | | |
| Median intrathecal methotrexate, mg (range) | 188.0 (9.2-721.4) | | |
| Cognitive function | | | |
| Mean visual-motor processing speed (SD) | −0.22 (0.96) | | |

NOTE. Data presented as No. (%) unless otherwise indicated. Smoking data for nine controls and diabetes data for 24 controls and four survivors were not available.
Abbreviation: SD, standard deviation.
*On the basis of current report for medication use.

interaction indicated that this association did not differ by survivor status ($P = .50$).

Survivors had lower mean values (Table 2) for dorsiflexion range of motion, plantar-flexor strength, and plantar-flexor endurance. Although more survivors than controls were classified as having impaired balance, the difference was not significant (11.5% *v* 7.5%; $P = .07$), and SOT mean scores between survivors and controls were not different. Survivors had lower mean scores

**Table 2.** Comparison of PN System Function, Static Balance, and Quality of Life Between Survivors and Controls

| Variable | Survivors | | Controls | | *P* |
|---|---|---|---|---|---|
| | Adjusted Mean | 95% CI | Adjusted Mean | 95% CI | |
| PN system function | | | | | |
| mTNS | 3.16 | 2.92 to 3.40 | 1.18 | 0.94 to 1.43 | < .001 |
| Ankle dorsiflexion ROM* (°) | 16.41 | 14.87 to 17.96 | 24.95 | 23.41 to 26.50 | < .001 |
| Ankle plantar flexion ROM* (°) | 110.94 | 109.27 to 110.42 | 112.09 | 110.41 to 113.76 | .270 |
| Ankle dorsiflexor strength* (Nm) | 50.55 | 48.24 to 52.86 | 50.75 | 48.45 to 53.06 | .890 |
| Ankle plantar flexor strength* (Nm) | 126.15 | 118.19 to 134.12 | 157.05 | 149.11 to 164.99 | < .001 |
| Ankle dorsiflexor endurance* (Nm) | 43.73 | 41.81 to 45.65 | 44.39 | 42.47 to 46.30 | .590 |
| Ankle plantar flexor endurance* (Nm) | 108.54 | 101.78 to 115.29 | 137.76 | 131.03 to 144.49 | < .001 |
| Static balance | | | | | |
| SOT score | 80.92 | 80.23 to 81.60 | 81.60 | 80.92 to 82.27 | .110 |
| Quality of life | | | | | |
| Physical functioning | 47.64 | 46.46 to 48.81 | 51.60 | 50.42 to 52.78 | < .001 |
| Role physical | 48.00 | 46.82 to 49.17 | 51.20 | 50.01 to 52.38 | < .001 |
| General health perceptions | 47.57 | 46.41 to 48.72 | 51.44 | 50.27 to 52.61 | < .001 |

NOTE. Data adjusted for height and smoking status. For correction of multiple comparisons, the critical α-level was set at .005.
Abbreviations: Nm, Newton-meter; PN, peripheral neuropathy; ROM, range of motion; SOT, Sensory Organization Test.
*Left and right sides combined.

on QoL measures than controls for physical functioning, role physical, and general health perceptions.

Survivors without PN had better performances on TUG, 6-minute walk test, and QoL than those with PN (Table 3). No difference was found in mean SOT scores among survivors with or without PN. These results were confirmed in multivariable analysis when controlling for age, sex, BMI, CRT, and VMPS; a lower score on the mTNS was associated with better performance on the TUG, the 6-minute walk test, and domains of QoL but not performance on SOT (Table 4). A better SOT score was associated with the absence of CRT and higher VMPS.

Performance on the SOT and sensory ratios are listed in Table 5 and stratified by static balance status and CRT. Survivors with impaired static balance had lower vision and vestibular ratios than those without impaired static balance. No difference was found in the mean somatosensory ratios among survivors with impaired and intact static balance. Similarly, no association was found between mTNS and any sensory ratio in survivors with impaired balance. However, VMPS was associated with vision ratio (Appendix Table A3, online only).

## DISCUSSION

To better understand the consequences of PN, we examined associations with static balance, mobility, walking endurance, and QoL in adult survivors of childhood ALL. Compared with individuals with no history of childhood cancer, ALL survivors were more likely to experience PN. PN was associated with poor mobility and QoL, albeit not with static balance impairments. Our analyses indicate that among ALL survivors, poorer VMPS is associated with static balance impairments, limited mobility, and poorer QoL and that those with impaired static balance have difficulty using both visual and vestibular inputs to maintain balance.

Forty percent of ALL survivors in this study had impaired peripheral sensation, motor function, or both. This rate is higher than previously reported in pediatric survivor populations. In a longitudinal study in pediatric survivors with non-CNS tumors, Gilchrist et al[29] observed that 11.5% of ALL survivors had PN 6-months after treatment. Jain et al[30] reported electrophysiologic and functional evidence of PN in 34% of childhood ALL survivors up to 3 years after chemotherapy, and Ramchandren et al[13] found nerve conduction abnormalities in approximately 30% of ALL survivors a mean of 7 years after treatment. These differences may be due to the older mean age of the participants in the current study or are related to the mTNS cut point we used to classify neuropathy. Our cut point for classifying neuropathy was less conservative than that used by others,[29] who used a score of $\geq 5$.

In older populations, diabetes and smoking may contribute to a higher prevalence of PN. In the current sample, only six survivors and four controls had diabetes at the time of assessment, so we could not examine the effect of diabetes on PN. Smoking status was associated with PN and may have contributed to the higher prevalence of PN in this study than in studies among pediatric ALL survivors who might be less likely to smoke.

In adjusted models, we did not find an association between mTNS and amount of anterior-posterior sway during a standing balance evaluation in our young adult population (mean age, 28 years). This finding contrasts that of studies with pediatric participants. In a study of 41 children with non-CNS malignances, Gilchrist and Tanner[31] reported that a higher score (more impairment) on the pediatric mTNS is associated with poorer performance on the balance subscale of the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition, which evaluates both static and dynamic balance, and includes such activities as standing on one leg and heel-toe walking. These activities require postural control during movement and may be more challenging than our test of static balance because impairments in muscle strength and general coordination are likely more important during movement than in quiet standing. It is also possible that the longer-term survivors in the current study have learned to compensate for PN over time. Participants in the Gilchrist and Tanner study were children evaluated during cancer treatment who may not have yet learned how to compensate for the effects of neuropathy on balance.

The current results are similar to some and differ from other studies of PN and balance in patients with adult-onset cancer. In a study of 29 adult patients with various cancer diagnoses, Vasquez et al[32] reported no association between mTNS and balance (using the Berg Balance Scale). In contrast, in a study of 20 patients with breast cancer treated with taxane-based chemotherapy, Wampler et al[21] identified an association between mTNS and performance on the SOT. One important difference between Wampler et al and our study is the severity of PN. Although the mean mTNS score in participants in the study by Wampler et al was 7, this value in the current study was 3. The survivors in the study by Wampler et al

**Table 3.** Static Balance, Mobility, and Quality of Life in Survivors of ALL Classified by PN

| | Survivors With PN* | | Survivors Without PN† | | Survivors With *v* Without PN | |
|---|---|---|---|---|---|---|
| Measure | Mean | SD | Mean | SD | Mean Difference | *P* |
| SOT score | 80.46 | 6.31 | 80.93 | 6.22 | −0.47 | .490 |
| TUG (seconds) | 5.88 | 2.29 | 5.16 | 1.13 | 0.71 | < .001 |
| 6-minute walk test (minute) | 552.30 | 93.60 | 600.43 | 88.34 | −48.13 | < .001 |
| Physical functioning | 44.30 | 13.50 | 50.50 | 8.75 | −6.20 | < .001 |
| Role physical | 44.80 | 14.57 | 50.80 | 8.51 | −6.00 | < .001 |
| General health perceptions | 45.88 | 11.71 | 49.58 | 9.72 | −3.70 | .002 |

NOTE. For correction of the multiple comparisons, the critical α-level was set at .008.
Abbreviations: ALL, acute lymphoblastic leukemia; PN, peripheral neuropathy; SD, standard deviation; SOT, Sensory Organization Test; TUG, Timed Up and Go.
*Those with a modified Total Neuropathy Score > 1.5 SDs of mean for age- and sex-specific comparison group.
†Those with a modified Total Neuropathy Score < 1.5 SDs of mean for age- and sex-specific comparison group.

  

**Table 4.** Associations Among Peripheral Neuropathy, Physical Performance, and Standardized (T-score) Quality of Life in Survivors of ALL

| | Sensory Organization Test | | | Timed Up and Go | | | 6-Minute Walk Test | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Estimate | 95% CI | *P* | Estimate | 95% CI | *P* | Estimate | 95% CI | *P* |
| Age | −0.03 | −0.15 to 0.09 | .600 | 0.01 | −0.02 to 0.04 | .580 | 0.90 | −0.71 to 2.50 | .270 |
| Female sex | −2.54 | −3.84 to −1.34 | < .001 | 0.63 | 0.28 to 0.98 | < .001 | −49.09 | −66.69 to −31.49 | < .001 |
| BMI | −0.01 | −0.11 to 0.09 | .830 | 0.02 | 0.00 to 0.05 | .080 | −4.66 | −5.96 to −3.36 | < .001 |
| CRT: yes | −1.57 | −2.98 to −0.16 | .030 | −0.02 | −0.40 to 0.36 | .910 | −7.70 | −26.78 to 11.39 | .430 |
| VMPS | 1.69 | 0.98 to 2.40 | < .001 | −0.54 | −0.74 to −0.35 | < .001 | 25.68 | 16.02 to 35.34 | < .001 |
| mTNS | −0.10 | −0.42 to 0.22 | .550 | 0.15 | 0.06 to 0.23 | .001 | −4.39 | −8.63 to −0.14 | .040 |
| Model $R^2$ | | 0.12 | | | 0.19 | | | 0.30 | |

| | Physical Functioning | | | Role Physical | | | General Health | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Estimate | 95% CI | *P* | Estimate | 95% CI | *P* | Estimate | 95% CI | *P* |
| Age | −0.39 | −0.59 to −0.19 | < .001 | −0.41 | −0.63 to −0.19 | < .001 | −0.26 | −0.47 to −0.06 | .010 |
| Female sex | −2.42 | −4.66 to 0.19 | .030 | −3.16 | −5.53 to 0.79 | .010 | −2.67 | −4.92 to −0.42 | .020 |
| BMI | −0.09 | −0.25 to 0.07 | .260 | −0.03 | −0.20 to 0.15 | .770 | −0.17 | −0.34 to −0.01 | .040 |
| CRT: yes | −1.15 | −3.56 to 1.27 | .350 | 0.71 | −1.85 to 3.27 | .590 | 0.76 | −1.67 to 3.20 | .540 |
| VMPS | 2.23 | 1.02 to 3.45 | < .001 | 3.15 | 1.87 to 4.42 | < .001 | 1.49 | 0.27 to 2.71 | .020 |
| mTNS | −1.33 | −1.79 to −0.87 | < .001 | −1.16 | −1.64 to −0.67 | < .001 | −0.88 | −1.34 to −0.42 | < .001 |
| Model $R^2$ | | 0.23 | | | 0.20 | | | 0.13 | |

NOTE. VMPS and history of CRT were weakly correlated ($r = -0.14$; $P = .01$), but this did not cause a multicollinearity issue in regression models. Separate regression analysis was performed for each dependent variable. All models included age, sex, BMI, CRT, VMPS, and mTNS.

Abbreviations: ALL, acute lymphoblastic leukemia; BMI, body mass index; CRT, cranial radiation therapy; mTNS, modified Total Neuropathy Score; VMPS, visual-motor processing speed.

were older (mean age, 50 ± 9 *v* 28 ± 6 years) than our survivors and were evaluated < 1 month after therapy completion.[33] Survivors in our cohort were ≥ 10 years since diagnosis, which again provided these participants with an opportunity to compensate for persistent impairment. Winter-Stone et al[34] found associations between self-reported symptoms of PN and number of falls reported in the past year in 512 female cancer survivors with a mean age of 62 years. They only used the presence of sensory symptoms to classify neuropathy, whereas we included motor signs and symptoms in the classification schema. In addition, their measure of balance was previous fall history, which reflects dynamic loss of postural control, whereas our measure, standing balance, was more static.

Although PN does not seem to be associated with impaired static balance, as determined by amount of anterior-posterior sway during static standing in long-term ALL survivors, it is associated with mobility. Our finding of an association between neuropathy and performance on the TUG is similar to that reported by Wampler et al[21] among patients with breast cancer in whom more severe PN was associated with longer time to complete the TUG. Conversely, Vasquez et al[32] reported no association between PN and performance on the TUG in adult patients with various cancer diagnoses. We also found an association between the mTNS and distance walked in 6 minutes, which were similar to those reported by Gilchrist and Tanner[35] who observed that scores on the pediatric mTNS explained 35% of the variability on the 6-minute walk test in 5- to 22-year-old patients with cancer. The associations between PN and mobility in the current study may indicate an association between PN and ability to maintain balance during movement not reflected in performance on the SOT.

Survivors with PN had lower mean scores on physical QoL measures than those without PN. The single previous study that examined this association in pediatric ALL survivors (age 8 to 18 years) found no association between PN measures and scores on the pediatric QoL inventory.[13] The association between PN and QoL has been investigated extensively in adult patients with cancer and survivors, where excellent reviews indicate that more-severe neuropathy predicts worse QoL.[36,37]

Although PN was not associated with the overall SOT score in our population, the analyses identified a potential mechanism for poor static balance and another contributor to impaired mobility and QoL among adult survivors of childhood ALL. VMPS was associated with performance on SOT, TUG, 6-minute walk test, and QoL. In addition, survivors who had impaired static balance did not seem to make use of visual and vestibular inputs to maintain standing when perturbed. These findings are similar to those reported by Einarsson et al,[38] who examined the effect of visual input on balance among adult survivors of pediatric solid tumors. These authors found that survivors had more difficulty than controls in maintaining standing when perturbed in an eyes open condition and concluded that survivors likely have difficulty with processing visual information. Although condition 2 on the SOT possibly was too easy for our sample of survivors, even those with impaired balance, these data suggest that static balance impairments in long-term survivors of ALL may be influenced by problems in CNS function, including the processing of visual and vestibular information.

The current results should be considered in the context of some study limitations. First, although the participation rate was excellent, not all eligible survivors participated. If those who agreed to participate were in better or worse health than those who did not agree to participate, study results could have been different. Furthermore, all the survivors included in this study were diagnosed with ALL between 1980 and 2003 and received their treatment at a single institution. Although the characteristics

**Table 5.** Scores From Each Condition of the SOT, Overall Score, and Sensory Ratios in Survivors Classified by Static Balance Impairment and History of CRT

| All Survivors (N = 353) | | | | | | |
|---|---|---|---|---|---|---|
| | Survivors With Impaired Balance (n = 42)* | | Survivors With Intact Balance (n = 311)† | | Impaired *v* Intact | |
| SOT Performance | Mean | SD | Mean | SD | Mean Difference | *P* |
| Condition 1 | 92.96 | 4.12 | 94.85 | 1.65 | −1.88 | .010 |
| Condition 2 | 88.49 | 5.44 | 91.80 | 2.89 | −3.31 | < .001 |
| Condition 3 | 87.19 | 6.65 | 90.85 | 3.22 | −3.66 | .001 |
| Condition 4 | 71.01 | 13.49 | 87.01 | 4.90 | −16.00 | < .001 |
| Condition 5 | 44.88 | 16.44 | 69.30 | 8.11 | −24.42 | < .001 |
| Condition 6 | 43.67 | 19.92 | 72.47 | 8.73 | −28.80 | < .001 |
| SOT score | 67.30 | 5.44 | 82.58 | 3.53 | −15.28 | < .001 |
| Vision ratio | 0.77 | 0.15 | 0.92 | 0.05 | −0.15 | < .001 |
| Somatosensory ratio | 0.95 | 0.08 | 0.97 | 0.03 | −0.01 | .250 |
| Vestibular ratio | 0.48 | 0.18 | 0.73 | 0.08 | −0.25 | < .001 |
| **Survivors Without CRT History (n = 207)** | | | | | | |
| | Survivors With Impaired Balance (n = 18)* | | Survivors With Intact Balance (n = 189)† | | Impaired *v* Intact | |
| SOT Performance | Mean | SD | Mean | SD | Mean Difference | *P* |
| Condition 1 | 93.83 | 1.81 | 94.90 | 1.62 | −1.07 | .010 |
| Condition 2 | 88.44 | 4.94 | 92.07 | 2.80 | −3.62 | .010 |
| Condition 3 | 88.42 | 5.61 | 91.03 | 3.19 | −2.61 | .070 |
| Condition 4 | 69.69 | 12.51 | 87.45 | 4.77 | −17.76 | < .001 |
| Condition 5 | 42.75 | 17.94 | 70.11 | 8.15 | −27.36 | < .001 |
| Condition 6 | 41.17 | 19.66 | 72.70 | 8.88 | −31.53 | < .001 |
| SOT score | 66.63 | 6.45 | 82.95 | 3.62 | −16.32 | < .001 |
| Vision ratio | 0.74 | 0.13 | 0.92 | 0.05 | −0.18 | < .001 |
| Somatosensory ratio | 0.94 | 0.05 | 0.97 | 0.03 | −0.03 | .030 |
| Vestibular ratio | 0.46 | 0.19 | 0.74 | 0.08 | −0.28 | < .001 |
| **Survivors With CRT history (n = 146)** | | | | | | |
| | Survivors With Impaired Balance (n = 24)* | | Survivors With Intact Balance (n = 122)† | | Impaired *v* Intact | |
| SOT Performance | Mean | SD | Mean | SD | Mean Difference | *P* |
| Condition 1 | 92.31 | 5.17 | 94.75 | 1.69 | −2.44 | .030 |
| Condition 2 | 88.52 | 5.90 | 91.38 | 2.99 | −2.86 | .030 |
| Condition 3 | 86.27 | 7.32 | 90.57 | 3.26 | −4.30 | .010 |
| Condition 4 | 72.00 | 14.36 | 86.32 | 5.04 | −14.32 | < .001 |
| Condition 5 | 46.48 | 15.43 | 68.06 | 7.92 | −21.58 | < .001 |
| Condition 6 | 45.56 | 20.33 | 72.12 | 8.53 | −26.57 | < .001 |
| SOT score | 67.80 | 4.64 | 82.00 | 3.23 | −14.21 | < .001 |
| Vision ratio | 0.78 | 0.17 | 0.91 | 0.05 | −0.13 | < .001 |
| Somatosensory ratio | 0.96 | 0.09 | 0.96 | 0.03 | 0.00 | .910 |
| Vestibular ratio | 0.50 | 0.17 | 0.72 | 0.08 | −0.21 | < .001 |

NOTE. For correction of multiple comparisons, the critical α-level was set at .005. SOT results were not available for 12 survivors.
Abbreviations: CRT, cranial radiation therapy; SD, standard deviation; SOT, Sensory Organization Test.
*Those with an SOT score > 1.5 SDs of mean for age- and sex-specific comparison group.
†Those with an SOT score < 1.5 SDs of mean for age- and sex-specific comparison group.

and CRT exposure for this population generally were similar to national protocols for childhood ALL during the same period, our findings may not be generalizable to individuals treated in other centers and with different treatment protocols. Finally, because not every child treated for ALL survived for 10 years after diagnosis, survival bias may have influenced the prevalence estimates and should not be extrapolated to populations whose survival is < 10 years.

Other methodological limitations also need to be considered when interpreting results. First, the medical needs of this complex study population prohibited blinding of study staff during measurement. Whenever possible, objective evaluation tools were used. Research personnel received extensive training, and intra- and interrater reliability testing was conducted before the start of the study and annually. Second, balance was measured by evaluating deviations in anterior-posterior sway during static standing. More dynamic balance assessment and gait analysis would enhance results. Third, although the validity of the mTNS has been evaluated for concordance with the total neuropathy score (a measure that includes nerve conduction velocity) in breast cancer survivors,[21] we did not include nerve conduction studies. Whether impairment determined with mTNS is associated with long-lasting abnormalities in nerve conduction in adult survivors of childhood ALL remains to be examined. Finally, we

  

used the digit symbol coding subset of the Wechsler Adult Intelligence Scale as a measure of VMPS, which is a paper-and-pen test. Poor performance could have been influenced by the presence of PN that affected hand function. However, because the prevalence of impaired hand function in our survivor sample was low, this influence was likely minimal.

In conclusion, mild or moderate PN is prevalent among adult survivors of childhood ALL and interferes with mobility and QoL but does not seem to be associated with static standing balance. The study provides evidence in favor of the application of contemporary neurorehabilitation approaches, such as cognitive-motor task training, to address functional problems in survivors. These strategies are effective in improving postural control in healthy individuals and in persons with neurologic impairment.[39,40] The current finding of associations among VMPS, balance, and mobility in survivors hints that a similar approach may be useful for remediating balance and mobility impairments in survivors of childhood ALL.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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**Peripheral Neuropathy, Sensory Processing, and Balance in Survivors of Acute Lymphoblastic Leukemia**

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## *Appendix*

**Table A1.** Description of PN Measured With mTNS in Survivors of ALL

| Measure | Survivors With PN | | | | Survivors Without PN | | | | Survivors With *v* Without PN |
|---|---|---|---|---|---|---|---|---|---|
| | Median | Mean | Maximum | SD | Median | Mean | Maximum | SD | *P* |
| Total sensory symptoms | 1 | 0.92 | 4 of 4 | 0.84 | 0 | 0.27 | 2 of 4 | 0.51 | < .001 |
| Total motor symptoms | 0 | 0.32 | 2 of 4 | 0.55 | 0 | 0.05 | 2 of 4 | 0.25 | < .001 |
| Hand | 0 | 0.17 | 3 of 4 | 0.54 | 0 | 0.05 | 2 of 4 | 0.29 | .020 |
| Foot | 0 | 0.27 | 4 of 4 | 0.72 | 0 | 0.03 | 2 of 4 | 0.20 | < .001 |
| Sensory neurologic examination | 0 | 0.63 | 8 of 8 | 1.43 | 0 | 0.08 | 2 of 8 | 0.29 | < .001 |
| Motor neurologic examination | 0 | 0.27 | 4 of 4 | 0.71 | 0 | 0.03 | 1 of 4 | 0.16 | < .001 |
| Total reflex score | 3 | 3.14 | 4 of 4 | 0.97 | 0 | 1.05 | 3 of 4 | 1.19 | < .001 |
| mTNS | 5 | 5.26 | 18 of 24 | 2.19 | 1 | 1.48 | 3 of 3* | 1.24 | < .001 |

NOTE. For correction of multiple comparisons, the critical α-level was set at .006.
Abbreviations: ALL; acute lymphoblastic leukemia; mTNS, modified Total Neuropathy Score; PN, peripheral neuropathy; SD, standard deviation.
*Although mTNS score ranges from 0 to 24, the maximum mTNS in survivors with intact balance was 3 because classification for PN was based on mTNS, and survivors with an mTNS ≥ 4 were classified as having PN.

**Table A2.** The Effect of Group Assignment (survivors *v* controls) on Peripheral Neuropathy Score Controlling for Height and Smoking Status

| Variable | Modified Total Neuropathy Score | | |
|---|---|---|---|
| | Estimate | 95% CI | P |
| Survivors group | 1.98 | 1.68 to 2.28 | < .001 |
| Height | −0.01 | −0.20 to 0.01 | .50 |
| Former smoker | 0.62 | 0.12 to 1.11 | .01 |
| Current smoker | 0.56 | 0.24 to 0.92 | .001 |

**Table A3.** Associations Among Peripheral Neuropathy and Sensory Ratios Derived From Performance on Sensory Organization Test in Survivors With Impaired Static Balance

| | Sensory Organization Test Score | | | Vision Ratio | | | Somatosensory Ratio | | | Vestibular Ratio | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | Estimate | 95% CI | *P* | Estimate | 95% CI | *P* | Estimate | 95% CI | *P* | Estimate | 95% CI | *P* |
| Age | −0.09 | −0.36 to 0.18 | .49 | 0.00 | −0.01 to 0.01 | .97 | −0.00 | −0.01 to 0.00 | .39 | 0.01 | −0.00 to 0.02 | .24 |
| Female sex | −3.59 | −7.69 to 0.51 | .08 | −0.12 | −0.24 to 0.00 | .06 | −0.04 | −0.11 to 0.03 | .24 | −0.03 | −0.17 to 0.11 | .65 |
| BMI | 0.23 | 0.04 to 0.50 | .10 | 0.01 | 0.00 to 0.02 | .01 | −0.00 | −0.01 to 0.00 | .10 | −0.01 | −0.02 to .003 | .15 |
| CRT: yes | 0.15 | −3.50 to 3.79 | .94 | 0.02 | −0.09 to 0.13 | .65 | 0.03 | −0.03 to 0.09 | .29 | −0.01 | −0.14 to 0.11 | .85 |
| VMPS | 2.52 | 0.36 to 4.69 | .02 | 0.07 | 0.00 to 0.13 | .04 | −0.00 | −0.04 to 0.03 | .88 | −0.00 | −0.08 to 0.07 | .97 |
| mTNS | −0.21 | −0.96 to 0.54 | .57 | 0.01 | −0.02 to 0.03 | .52 | 0.01 | −0.01 to 0.02 | .36 | 0.00 | −0.02 to 0.03 | .75 |
| Model $R^2$ | | 0.26 | | | 0.30 | | | 0.15 | | | 0.13 | |

NOTE. A separate regression analysis was performed for each dependent variable. All models included age, sex, BMI, CRT, VMPS, and mTNS.
Abbreviations: BMI, body mass index; CRT, cranial radiation therapy; mTNS, modified Total Neuropathy Score; VMPS, visual-motor processing speed.